REMARKS

The Status of the Claims.

Claims 28, 29, and 36 to 46 are allowed.

The Examiner has noted that lines representing bonds in many formulae of the specification and figures are not dark. Replacement Sheets for Figures 1 and 2 and for specification pages 5, 13-15, 17, 20-22, 24 and 26-28 have been requested with darker lines in the chemical structures. These Replacement sheets for all of the original Figures and requested specification pages (plus page 14 which has a structure) are attached as an Appendix to this document.

Applicants submit that the Replacement Sheets merely sharpen and intensify lines on the sheets without addition of any new matter.

CONCLUSION

Applicants appreciate the Notice of Allowance for the current claims. If the present document is not fully responsive to the Examiner's Comments Applicants request the Examiner contact the undersigned at (510) 769-3510 so any deficiencies can be promptly addressed.

QUINE INTELLECTUAL PROPERTY LAW GROUP
P.O. BOX 458, Alameda, CA 94501
Tel: 510 769-3510
Fax: 510 337-7877
PTO Customer No.: **22798**
Deposit Account No.: **50-0893**

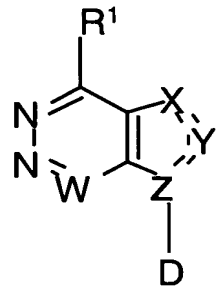
Respectfully submitted,

Gary Baker
Reg. No: 41,595

Attachments:

1) Appendix of Replacement Sheets;
2) Letter to Draftsperson;
3) Replacements Figures 1-6 and,
4) A receipt indication postcard.

wherein

Formula I 

W is selected independently from X, Y and Z from the group consisting of N and CR^2,

Z is selected from the group consisting of N and C with the proviso that

- if Z is N, then

  X independently from W and Y is selected from the group consisting of N and CR^3, and

  Y independently from W and X is selected from the group consisting of N and CR^4,

  and the bond between X and Y is a double bond and the bond between Y and Z is a single bond, and

- if Z is C, then

  X is NR^{33}, and

  Y is selected from the group consisting of N and CR^4 and

  the bond between Z and Y is a double bond and the bond between X and Y is a single bond,

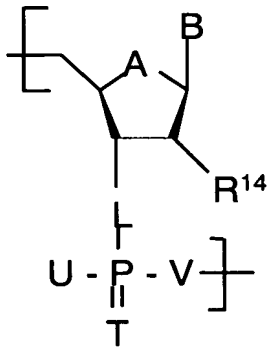
R^1, R^2, R^3 and R^4 are independently selected from the group consisting of -H, -halogen, $-OR^{13}$, $-SR^{19}$, $-(C_1-C_{10})$-alkyl, $-(C_2-C_{10})$-alkenyl, $-(C_2-C_{10})$-alkynyl, $-NO_2$, $-NR^5R^6$, -cyano, and $-C(=O)R^{11}$,

base sequences being preferred.

The nucleic acid binding compound according to the invention will bind to nucleic acids preferably in the antiparallel mode. However, by carefully selecting the nucleobases of a nucleic acid and/or of the nucleic binding compound, the binding can also be forced to be in the parallel mode. Parallel hybridization of nucleic acids containing iso-C and iso-G are for example disclosed in EP 0 624 161.

Preferred nucleic acid binding compounds are those, wherein the backbone comprises one or more moieties of the general formula II

Formula II



wherein

A is selected from the group consisting of O, S and N-(C_1-C_{10})-alkyl,

L is selected from the group consisting of oxy, sulfanediyl and -NR^{22}-,

T is selected from the group consisting of oxo, thioxo and selenoxo,

U is selected from the group consisting of -OH, -O-reporter group, -SH, -S reporter group -SeH, -(C_1-C_{10})-alkoxy, (C_1-C_{10})-alkyl, -(C_6-C_{22})-aryl, -(C_6-C_{14})-aryl-(C_1-C_{10})-alkyl, -$NR^{23}R^{24}$, and -O-(C_1-C_{10})-alkyl-O-(C_1-C_{10})-alkyl-R^{25}, or wherein -$NR^{23}R^{24}$ can together with N be a 5-6-membered heterocyclic ring,

V is selected from the group consisting of oxy, sulfanediyl or -NR^{22}-,

R^{14} is selected from the group consisting of -H, -OH, -(C_1-C_{10})-alkoxy, -(C_2-C_{10})-alkenyloxy, -halogen, -azido, -O-allyl, -O-alkinyl, and -NH_2,

R^{22} is independently selected from the group of –H and -(C_1-C_{10})-alkyl,

R^{23} and R^{24} are independently selected from the group consisting of -(C_1-C_{10})-alkyl, -(C_1-C_{20})-aryl, -(C_6-C_{14})-aryl-(C_1-C_{10})-alkyl, -(C_1-C_6)-alkyl-$[NH(CH_2)_c]_d$-$NR^{26}R^{27}$ and a reporter group,

R^{25} is selected from the group consisting of -H, -OH, -halogen, -amino, -(C_1-C_{18})-alkylamino, -COOH, -$CONH_2$ and -$COO(C_1$-$C_4)$-alkyl and a reporter group,

R^{26} and R^{27} are independently selected from the group consisting from -H, -(C_1-C_6)-alkyl, and -(C_1-C_4)-alkoxy-(C_1-C_6)-alkyl and a reporter group,

c is an integer from 2 to 6,

d is an integer from 0 to 6, and

B is a moiety of formula I,

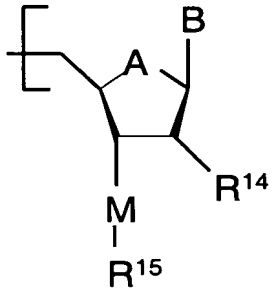
wherein any alkyl, alkenyl and alkynyl can be substituted or unsubstituted,

and any salts thereof.

The preferred definitions of the groups as defined under formula I apply to formula II and the following formulae, if not indicated otherwise.

A preferred subject of the invention is therefore a nucleic acid binding compound as outlined above, wherein the backbone comprises one or more moieties of the general formula III

Formula III



wherein

A is selected from the group consisting of O, S and N-(C_1-C_6)-alkyl,

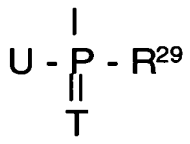
M is selected from the group consisting of oxy, sulfanediyl, -NR^{22}-, -(C_1-C_{10})-alkyl-, or -O-(C_1-C_{10})-alkyl-O-, and -S-(C_1-C_{10})-alkyl-O- and -NR^{22}-(C_1-C_6)-alkyl-O-,

R^{22} is selected from the group of –H, -(C_1-C_{10})-alkyl, a protecting group and a reporter group,

R^{14} is selected from the group consisting of -H, -OH, -(C_1-C_{10})-alkoxy, -(C_2-C_{10})-alkenyloxy, -(C_2-C_{10})-alkynyloxy, -halogen, -azido, SH, -(C_1-C_{10})-alkylmercapto and -NH_2,

R^{15} is selected from the group consisting of -H, -(C_1-C_6)-alkyl, -(C_2-C_{10})-alkenyl, -(C_2-C_{10})-alkynyl, -(C_2-C_{10})-alkyl-carbonyl, -(C_3-C_{19})-alkenyl-carbonyl, -(C_3-C_{19})-alkynyl-carbonyl, -(C_6-C_{14})-aryl-(C_1-C_{10})-alkyl, a solid phase and a group of formula IV

Formula IV



wherein

T is selected from the group consisting of oxo, thioxo and selenoxo, and

U is selected from the group consisting of -OH, -O-reporter group, -SH, -SeH, -(C_1-C_{10})-alkoxy, -(C_1-C_{10})-alkyl, -(C_6-C_{22})-aryl, -(C_6-C_{14})-aryl-(C_1-C_{10})-alkyl, -$NR^{23}R^{24}$, and -O-(C_1-C_{10})-alkyl-O-(C_1-C_{10})-alkyl-R^{25}, or wherein $NR^{23}R^{24}$ can together with N be a 5-6-membered heterocyclic ring,

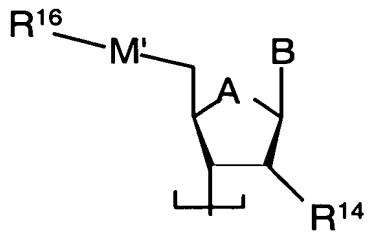
R^{23} and R^{24} are independently selected from the group consisting of -(C_1-C_{10})-alkyl, -(C_1-C_{20})-aryl, -(C_6-C_{14})-aryl-(C_1-C_{10})-alkyl, -(C_1-C_6)-alkyl-$[NH(CH_2)_c]_d$-$NR^{26}R^{27}$,

R^{25} is selected from the group consisting of -H, -OH, -halogen, -amino, -(C_1-C_{18})-alkylamino, -COOH, -$CONH_2$ and -$COO(C_1$-$C_4)$-alkyl,

R^{26} and R^{27} are independently selected from the group consisting from -H, -(C_1-C_6)-alkyl, and -(C_1-C_4)-alkoxy-(C_1-C_6)-alkyl

R^{29} is selected from the group consisting of -OR^{30} and -SR^{30},

A preferred subject of the invention is a nucleic acid binding compound as outlined above comprising a backbone moiety of the formula V

Formula V 

wherein

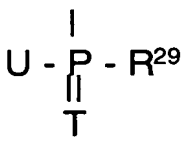
A is selected from the group consisting of O, S and N-(C_1-C_6)-alkyl,

M' is selected from the group consisting of oxy, sulfanediyl, -NR^{22}-, -(C_1-C_{10})-alkyl, or -O-(C_1-C_{10})-alkyl-O-, and -S-(C_1-C_{10})-alkyl-O- and -NR^{22}-(C_1-C_6)-alkyl-O-,

R^{22} is selected from the group of -H, a protecting group, a reporter group and -(C_1-C_{10})-alkyl,

R^{14} is selected from the group consisting of -H, -OH, -(C_1-C_{10})-alkoxy, -(C_2-C_{10})-alkenyloxy, -(C_2-C_{10})-alkynyloxy, -halogen, azido, -SH, -S-(C_1-C_6)-alkylmercapto and NH_2,

R^{16} is selected from the group consisting of -H, -(C_1-C_8)-alkyl, -(C_2-C_{18})-alkenyl, -(C_2-C_{18})-alkynyl, -(C_2-C_{18})-alkyl-carbonyl, -(C_3-C_{19})-alkenyl-carbonyl, -(C_3-C_{19})-alkynyl-arbonyl, -(C_6-C_{14})-aryl-(C_1-C_8)-alkyl, a protective group or a compound of formula IV

Formula IV 

wherein

T is selected from the group consisting of oxo, thioxo and selenoxo,

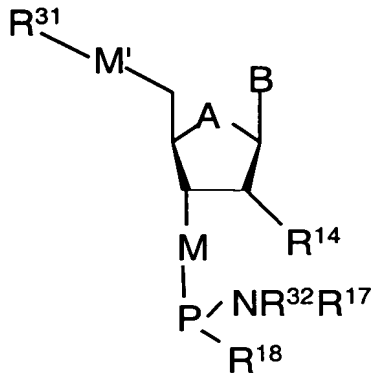
U is selected from the group consisting of -OH, -SH, -SeH, -(C_1-C_{10})-alkoxy, -(C_1-C_{10})-alkyl, -(C_6-C_{22})-aryl, -(C_6-C_{14})-aryl-(C_1-C_{10})-alkyl, -$NR^{23}R^{24}$, and

The predetermined substituents are preferably selected from the group of $-NH_2$, -SH and -OH.

A further subject of the invention is therefore a method for the chemical synthesis of a compound of any of claims 1 to 13 using activated subunits, wherein said subunit contains at least one group of formula I. There are several approaches known for the chemical synthesis, such as the phosphotriester method of Narang et al., Meth. Enzymol. 68, 90-99 (1979); the phosphodiester method of Brown et al., Meth. Enzymol. 68, 109-151 (1979); the diethylphosphoramidite method of Beaucage et al., Tetrahedron Lett. 22, 1859-1862 (1981); and the solid support method described in the U.S. Patent Specification No. 4,458,066 and in Methods in Molecular Biology, Ed. S. Agrawal, Vol. 20, Humana Press, Totowa, NJ, 1993. The most preferred method of chemical synthesis uses the phosphoramidite approach. A particularly preferred method uses a activated subunit one or more compounds of general formula VII. This method has the advantage that it is very convenient and the reagents necessary, for example a phosphoramidite containing a group of formula I, is possible to be included easily.

A further subject of the invention are therefore compounds of the general formula VII

Formula VII



wherein

A is selected from the group consisting of O, S and N-(C_1-C_6)-alkyl,

M and M' are independently selected from the group consisting of oxy, sulfanediyl, $-NR^{22}$, -(C_1-C_{10})-alkyl, or -O-(C_1-C_{10})-alkyl-O-, and -S-(C_1-C_{10})-alkyl-O- and $-NR^{22}$-(C_1-C_6)-alkyl-O-,

R^{22} is selected from the group of -H and -(C_1-C_{10})-alkyl,

R^{14} is selected from the group consisting of -H, -OR^{31}, -(C_1-C_{10})-alkoxy, -(C_2-C_{10})-alkenyloxy, -(C_2-C_{10})-alkynyloxy, -halogen, -azido NHR^{31}, SR^{31} and -NH_2,

R^{31} is a protecting group or a reporter group,

R^{32} and R^{17} are independently selected from the group consisting of -H, -(C_1-C_{10})-alkyl, -(C_2-C_{10})-alkenyl and -(C_6-C_{22})-aryl,

R^{18} is selected from the group consisting of substituted or unsubstituted -(C_1-C_6)-alkyl, unsubstituted -(C_1-C_6)-alkoxy or -(C_1-C_6)-alkoxy substituted one or more times by a group selected from the group consisting of -halogen, p-nitroaryloxy and -cyano, and

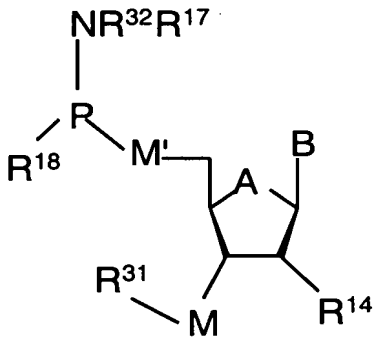
B is a group of formula I.

Preferred compounds of formula VII are those wherein the group of formula I is not 2-aza-hypoxanthine. In a preferred embodiment, the group of formula I in formula VII contains at least one reporter group. Most preferable, the group of formula I contains exactly one reporter group.

Most preferred in such compounds, in -NR^5R^6 at least one of R^5 and R^6 is a protecting group.

Further subject of the invention are compounds of general formula IX

Formula IX



wherein

A is selected from the group consisting of O, S and N-(C_1-C_6)-alkyl,

M and M' are independently selected from the group consisting of oxy, sulfanediyl, -NR^{22}, -(C_1-C_{10})-alkyl, or -O-(C_1-C_{10})-alkyl-O-, and -S-(C_1-C_{10})-alkyl-O- and -NR^{22}-(C_1-C_6)-alkyl-O-,

R^{22} is selected from the group of -H and -(C_1-C_{10})-alkyl,

R^{14} is selected from the group consisting of -H, -OR^{31}, -(C_1-C_{10})-alkoxy, -(C_2-C_{10})-alkenyloxy, -(C_2-C_{10})-alkynyloxy, -halogen, -azido NHR^{31}, SR^{31} and -NH_2,

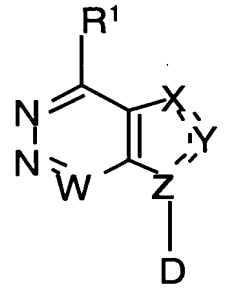
R^{31} is a protecting group or a reporter group,

R^{32} and R^{17} are independently selected from the group consisting of -H, -(C_1-C_{10})-alkyl, -(C_2-C_{10})-alkenyl and -(C_6-C_{22})-aryl,

R^{18} is selected from the group consisting of substituted or unsubstituted -(C_1-C_6)-alkyl, unsubstituted -(C_1-C_6)-alkoxy or -(C_1-C_6)-alkoxy substituted one or more times by a group selected from the group consisting of -halogen, p-nitroaryloxy and -cyano, and

B is a group of formula I

Formula I



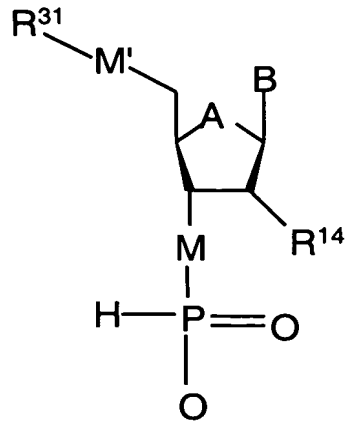
wherein

W is selected independently from X, Y and Z from the group consisting of N and CR^2,

Z is selected from the group consisting of N and C with the proviso that

- if Z is N, then

Formula X



wherein

M and M' are independently selected from the group consisting of oxy, sulfanediyl, $-NR^{22}$, $-(C_1-C_{10})$-alkyl, or $-O-(C_1-C_{10})$-alkyl-O-, and $-S-(C_1-C_{10})$-alkyl-O- and $-NR^{22}-(C_1-C_6)$-alkyl-O-,

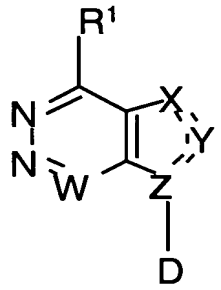
R^{22} is selected from the group of -H and $-(C_1-C_{10})$-alkyl,

R^{14} is selected from the group consisting of -H, $-OR^{31}$, $-(C_1-C_{10})$-alkoxy, $-(C_2-C_{10})$-alkenyloxy, $-(C_2-C_{10})$-alkynyloxy, -halogen, -azido NHR^{31}, SR^{31} and $-NH_2$,

R^{31} is a protecting group or a reporter group,

B is a group of formula I

Formula I



wherein

W is selected independently from X, Y and Z from the group consisting of N and CR^2,

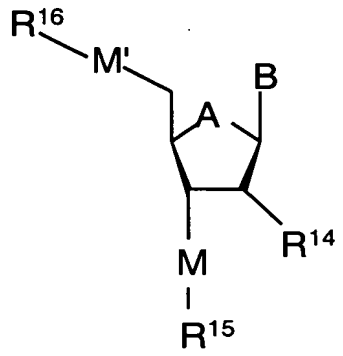
In another option which is more suited for long oligomers and those based on natural backbones, the oligomers are produced enzymatically. In this case, a starting oligomer is reacted with a polymerase and a triphosphate or modified triphosphate such that a monophoshate or a modified monophosphate is attached to a terminus of the oligomer, thus elongating the oligomer. Also for this method, the man skilled in the art will know several possible formates, like the nick-translation approach, or the simple primer extension (J. Sambrook. E.F. Fritsch, T. Maniatis, Molecular Cloning - A laboratory Manual, Cold Spring Harbor Laboratory Press 1989).

For example, the incorporation of z^2A_d into a DNA sequence can be performed via conventional methods, e.g. by polymerase-catalyzed incorporation of z^2A_d-5'-triphosphate (**11**).

A further subject of the invention is therefore a method for the enzymatic synthesis of a nucleic acid binding compound according to the invention comprising reacting a triphosphate subunit with a primer using a nucleic acid as a template for the elongation of the primer, wherein the triphosphate subunit contains a heterocyclic group of formula I. Preferably, the triphosphate subunit has the formula VI.

A further subject of the present invention are therefore compounds of the general formula VI

Formula VI



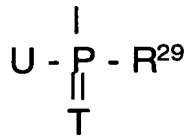
wherein

A is selected from the group consisting of O, S and N-(C_1-C_6)-alkyl,

R^{14} is selected from the group consisting of -H, -OH, -(C_1-C_{10})-alkoxy, O-protecting group, S-protecting group, NH-protecting group, -(C_2-C_{10})-alkenyloxy, -halogen, -azido, -SH, -(C_1-C_6)-alkylmercapto and -NH_2,

R^{15} and R^{16} are independently selected from the group consisting of -H, -(C_1-C_8)-alkyl, -(C_2-C_{18})-alkenyl, -(C_2-C_{18})-alkynyl, -(C_2-C_{18})-alkyl-carbonyl, -(C_3-C_{19})-alkenyl-carbonyl, -(C_3-C_{19})-alkynyl-carbonyl, -(C_6-C_{14})-aryl-(C_1-C_8)-alkyl, a protecting group or a compound of formula IV

Formula IV



wherein

T is selected from the group consisting of oxo, thioxo and selenoxo,

U is selected from the group consisting of -OH, -SH, -SeH, -(C_1-C_{10})-alkoxy, -(C_1-C_{10})-alkyl, -(C_6-C_{22})-aryl, -(C_6-C_{14})-aryl-(C_1-C_{10})-alkyl, -$NR^{23}R^{24}$, and -O-(C_1-C_{10})-alkyl-O-(C_1-C_{10})-alkyl-R^{25}, or wherein $NR^{23}R^{24}$ can together with N be a 5-6-membered heterocyclic ring,

R^{23} and R^{24} are independently selected from the group consisting of -(C_1-C_{10})-alkyl, -(C_1-C_{20})-aryl, -(C_6-C_{14})-aryl-(C_1-C_{10})-alkyl, -(C_1-C_6)-alkyl-$[NH(CH_2)_C]_d$-$NR^{26}R^{27}$,

R^{25} is selected from the group consisting of -H, -OH, -halogen, amino, -(C_1-C_{18})-alkylamino, -COOH, -$CONH_2$ and $COO(C_1$-$C_4)$-alkyl,

R^{26} and R^{27} are independently selected from the group consisting from -H, -(C_1-C_6)-alkyl, and -(C_1-C_4)-alkoxy-(C_1-C_6)-alkyl,

R^{29} is selected from the group consisting of -OR^{30} and -SR^{30},

R^{30} is selected from the group consisting of -H, -(C_1-C_{10})-alkyl, -(C_2-C_{10})-alkenyl, -(C_6-C_{22})-aryl, a protecting group, a diphosphate and a reporter group, and

M and M' are independently selected from the group consisting of oxy, sulfanediyl, -NR^{22}, -(C_1-C_{10})-alkyl, or -O-(C_1-C_{10})-alkyl-O-, and -S-(C_1-C_{10})-alkyl-O- and -NR^{22}-(C_1-C_6)-alkyl-O-,

R^{22} is selected from the group of -H and -(C_1-C_{10})-alkyl, and

B is a moiety of formula I,

wherein any alkyl, alkenyl and alkynyl can be substituted or unsubstituted, and wherein at least one of R^{15} and R^{16} is not a group of formula IV with the proviso that

MR^{16}, MR^{15} and R^{14} are not each -OH if R^1 is $-NH_2$ and if either

- W and X and Y and Z is N, or
- W and X and Z is N and Y is CR^4, or
- W and Y and Z is N and X is CR^3.

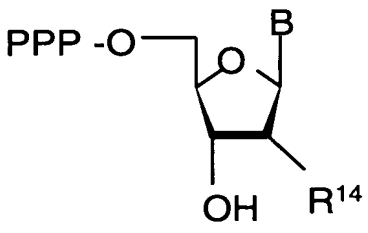
Most preferred in these compounds $-MR^{16}$ is a triphosphate group and $-MR^{15}$ is OH. The most preferred compound is the one in which R^{14} is -OH.

Those compounds are especially the compounds, wherein the heterocyclic moiety of the invention is contained not at the terminal position of the nucleic acid binding compound.

Preferred compounds are those, wherein M is oxy or sulfanediyl, R^{16} is a compound of formula IV wherein U is -OH, T is oxo or thioxo, R^{29} is $-OR^{30}$ and R^{30} is a disphosphate group and the salts thereof.

Most preferred compounds are of formula VIII

Formula VIII



wherein

PPP is a triphosphate group,

R^{14} is selected from the group consisting of -H, -OH, $-(C_1-C_{10})$-alkoxy, $-(C_2-C_{10})$-alkenyloxy, $-(C_2-C_{10})$-alkynyloxy halogen, -azido and NH_2, and